PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

19 OCT 2004

Applicant's or agent's file reference 8426-1650PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA 03/00838	International filing date *(day/month/year)* 02.06.2003	Priority date *(day/month/year)* 06.06.2002
International Patent Classification (IPC) or both national classification and IPC A61P27/06		
Applicant MERCK FROSST CANADA & CO. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.11.2003	19.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Johnson, C Telephone No. +49 89 2399-8287

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA 03/00838

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-50 as originally filed

Claims, Numbers

1-26 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1,10,17,20,21,23,24 (all part)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1,10,17,20,21,23,24 (all part) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 1,10,17,20,21,23,24 (all part) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13,15-22
	No:	Claims	14,23-25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26
Industrial applicability (IA)	Yes:	Claims	17-26 Yes
	No:	Claims	

2. Citations and explanations

   see separate sheet

III. Non-establishment of opinion

The term "prodrug" is not considered to fulfil the requirements of Articles 5 and 6 PCT. The search was therefore made based on the compounds of formula I, their pharmaceutically acceptable salts, enantiomers, diastereomers and mixtures thereof and the methods of use thereof. The following examination has been carried out for searched subject matter only.

Claims 1-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V. Reasoned statement

Reference is made to the following documents:
D1: WO-A-0224647
D2: WO-A-0242268
D3: WO-A-0038667
D4: WO-A-0038663

Novelty

D1 describes the use of compounds of formula (I) as i.a. neuroprotective agents (see Derwent abstract, subheading "Activity"). It is noted that the applicant disputes the fact that D1 does in fact disclose this use, as neither the English language abstract of the international publication pamphlet nor the "use" section of the Derwent abstract mention it. The applicant has not shown that the original Japanese language patent disclosure itself does not mention this use. There is thus no reason to doubt that the information contained in the Derwent abstract is correct. It is not unusual that the abstract of the international publication and that of Derwent differ somewhat in content, and it is common that the Derwent abstract contains more information. Formula (I) of D1 overlaps with present formula I. D1 is thus novelty-destroying for claims 14, and 23-25. Claims 14 and 23-25 therefore do not fulfil the requirements of Article 33(2) PCT.

The subject matter of D2 differs from that presently claimed because there is no difluoromethylene group adjacent to the hydroxymethylene group in the compounds of formula I. D3 and D4 do not relate to pyrrolidone derivatives.

Inventive step

D3 describes compounds for use in the treatment of glaucoma or ocular hypertension. The technical problem underlying present claims 1-13, 20-22 is the provision of further methods and pharmaceutical compositions for treating glaucoma or ocular hypertension. D3 states that EP_4 receptor agonists may be useful to lower intraocular pressure (p. 10, l. 6-10 - "potent and/or selective activation of the trabecular meshwork EP_4 receptors might yield a more efficacious lowering of IOP"). The applicant has objected that D3 contains a clear indication that not all EP_4 receptor agonists will have the utility. A passage in D3 confirming this statement has not been identified. It would therefore be obvious to attempt to solve the above-formulated technical problem, with a reasonable expectation of success, by replacing the EP_4 agonists of D3 by other compounds known to be EP_4 agonists.

D1 presents compounds of formula (I) as being EP_4 agonists. Using compounds of D1 in a method of lowering intraocular pressure is therefore obvious in the light of D1 combined with D3. D3 also states that the EP_4 agonists can be combined with further active ingredients such as beta-blockers (p. 4, l. 9-16). Claims 1-13, 20-22 therefore do not fulfil the requirements of Article 33(3) PCT.

D1 describes compounds as i.a. neuroprotective agents. The technical problem underlying present claims 14-16, 23-25 is the provision of further methods and pharmaceutical compositions for providing neuroprotection. Solving this problem by using compounds of D1 or their obvious alternatives does not require inventive skill. Claims 14-16, 23-24 therefore do not fulfil the requirements of Article 33(3) PCT.

The technical problem underlying present claims 17-19 is the provision of further EP_4 agonists. D1 may be considered the closest prior art. The present compounds differ from those of D1 because of the tetrazole group in place of e.g. a carboxyl group. D2 demonstrates the equivalence of tetrazole and carboxyl groups in compounds with EP_4 agonist activity. It would thus be obvious to apply the teaching of D2 to the compounds of D1 and hence to arrive at the present subject matter. The applicant has argued that, based on the teachings of D1 and D2, one could move in numerous directions. However, the fact that there are many possibilities does not make the choice of a single, arbitrarily chosen possibility inventive. There is no indication that the choice is not arbitrary, i.e. that the chosen group of compounds has a particular activity not to be expected from the teaching

of D1 or D2. Claims 17-26 thus do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 17-26 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claims 1-16 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.